US006841578B2

(12) **United States Patent**
Sonis

(10) **Patent No.: US 6,841,578 B2**
(45) **Date of Patent: Jan. 11, 2005**

(54) **TREATMENT AND PREVENTION OF MUCOSITIS IN CANCER PATIENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/222,539**

(22) Filed: **Aug. 16, 2002**

(65) **Prior Publication Data**

US 2003/0064913 A1 Apr. 3, 2003

Related U.S. Application Data

(60) Provisional application No. 60/352,674, filed on Jan. 29, 2002, and provisional application No. 60/313,081, filed on Aug. 16, 2001.

(51) **Int. Cl.**[7] **A61K 31/45**
(52) **U.S. Cl.** **514/728**; 514/724
(58) **Field of Search** 514/724, 728

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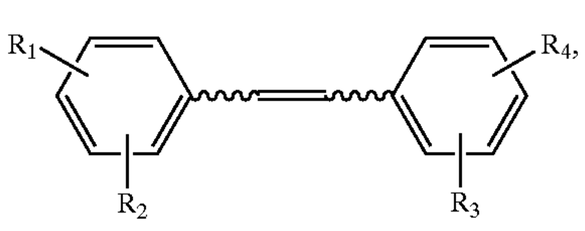
(57) **ABSTRACT**

The invention features a method for the treatment or prevention of mucositis in an individual undergoing or preparing to undergo cancer treatment. The method includes administering a therapeutically effective amount of an inhibitor of NF-κB to an individual undergoing or preparing to undergo a treatment for cancer. In certain embodiments, the inhibitor is a compound having the formula:



(I)

where R_1 and R_4 are OH, and R_2 and R_3 are independently OH or H, provided that when R_1 and R_2 are both OH, R_1 and R_2 cannot be disposed ortho to one another, and when R_3 and R_4 are both OH, R_3 and R_4 cannot be disposed ortho to one another. The compounds of formula I may be cis or trans.

12 Claims, 4 Drawing Sheets

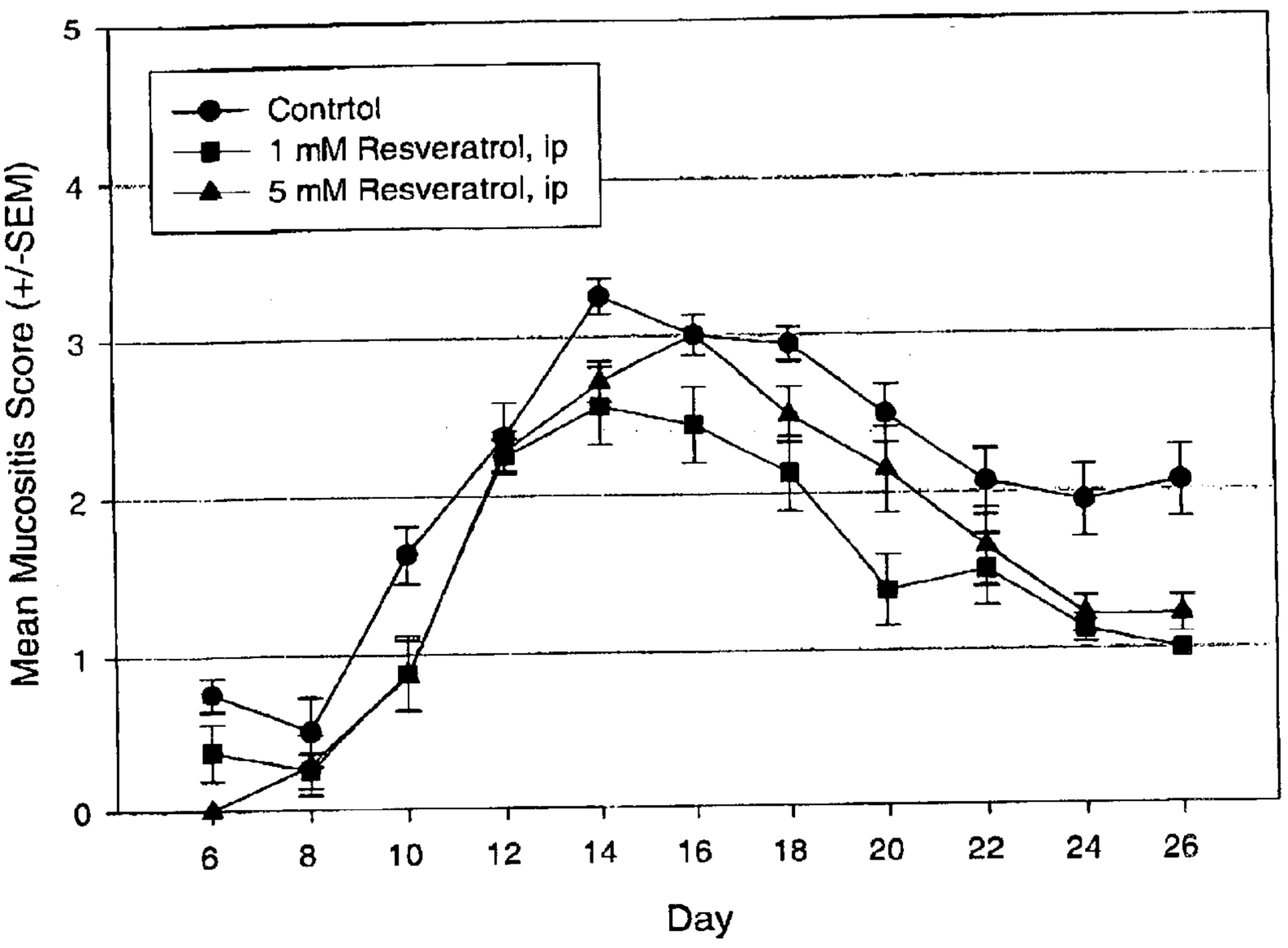

Contrtol
1 mM Resveratrol, ip
5 mM Resveratrol, ip
Mean Mucositis Score (+/-SEM)
0
1
2
3
4
5
6
8
10
12
14
16
18
20
22
24
26
Day

FIG. 1

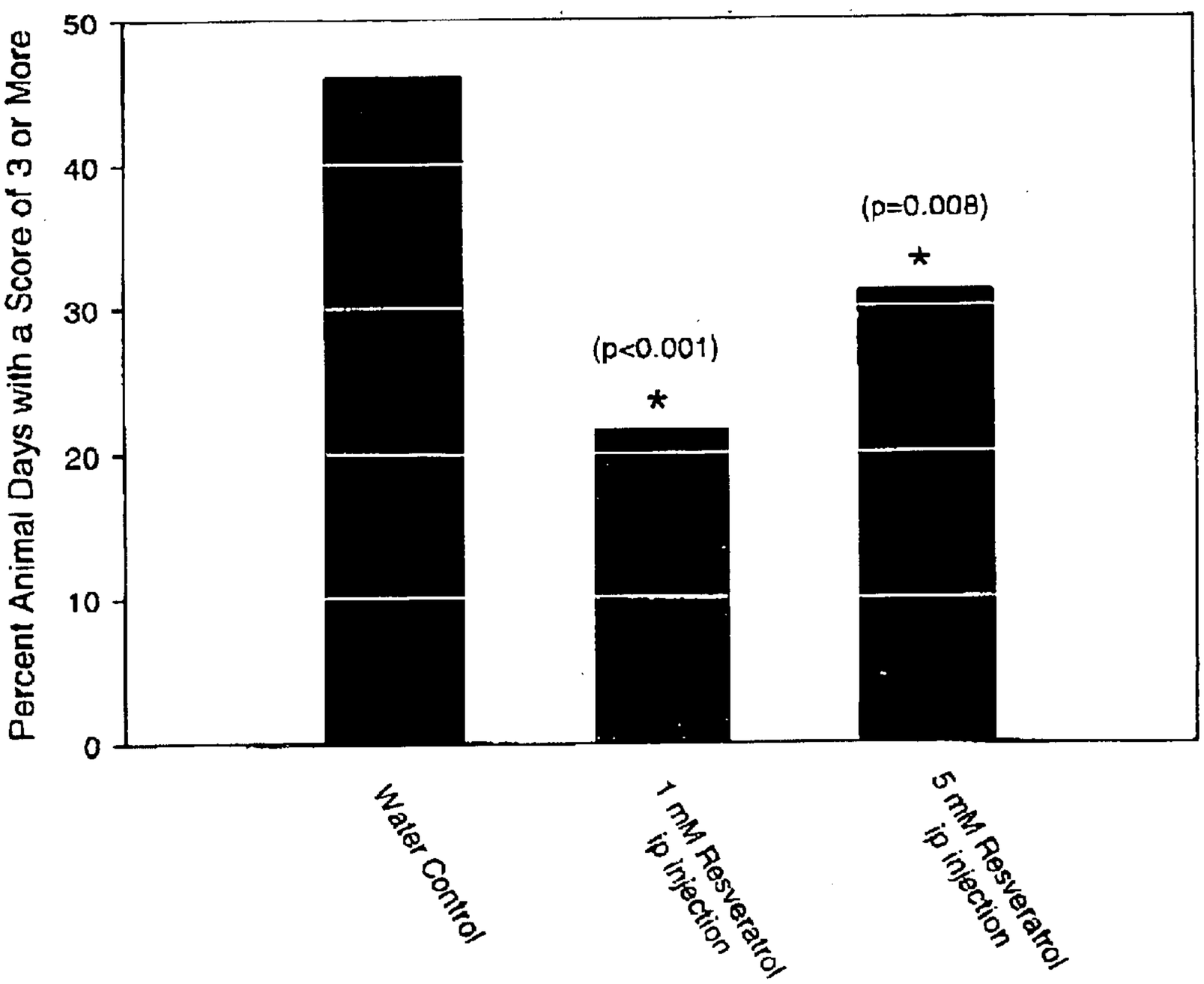

Percent Animal Days with a Score of 3 or More
50
40
30
20
10
0
(p<0.001)
*
(p=0.008)
*
Water Control
1 mM Resveratrol ip injection
5 mM Resveratrol ip injection

FIG. 2

Group	Days >=3	Days<3	Total Days	% Days >=3	Chi Sq v Control	P Value
Water Control	81	95	176	46.0	---	---
1 mM Resveratrol, ip	38	138	176	21.6	19.139	<0.001
5 mM Resveratrol, ip	48	106	154	31.2	7.000	0.008

FIG. 3

Group	Animal	6	8	10	12	14	16	18	20	22	24	26
1	1	0	2	3	4	4	4	3	2	2	2	2
		0	2	3	4	4	4	4	2	2	2	2
1	2	1	0	1	1	3	3	3	3	2	2	3
		1	0	1	1	3	3	3	3	1	1	2
1	3	1	0	2	2	3	3	3	3	3	3	3
		1	0	2	2	3	3	3	3	3	3	3
1	4	1	0	1	2	3	3	3	3	3	3	3
		1	0	1	2	3	3	3	3	3	3	3
1	5	0	0	2	2	3	3	3	3	2	1	1
		0	0	2	2	3	3	3	3	1	1	1
1	6	1	2	2	3	3	3	3	2	2	1	1
		1	2	2	3	4	3	3	2	1	1	1
1	7	1	0	1	2	3	2	2	1	1	1	1
		1	0	1	2	3	2	2	1	1	1	1
1	8	1	0	1	3	3	3	3	3	3	3	3
		1	0	1	3	4	3	3	3	3	3	3
2	9	1	0	1	2	3	3	3	1	3	1	1
		1	0	1	2	4	3	3	1	3	1	1
2	10	0	1	2	3	3	2	1	1	1	1	1
		0	1	2	3	3	2	1	1	1	1	1
2	11	0	0	0	2	3	4	3	3	3	2	1
		0	0	0	2	3	4	3	4	3	2	1
2	12	0	0	0	2	3	3	3	1	1	1	1
		0	0	0	2	3	3	3	1	1	1	1
2	13	0	0	0	2	3	3	3	1	1	1	1
		0	0	0	2	3	3	3	1	1	1	1
2	14	0	0	2	2	3	2	2	1	1	1	1
		0	0	2	2	3	1	2	2	1	1	1
2	15	0	1	0	2	1	2	1	1	1	1	1
		0	1	0	2	1	2	1	1	1	1	1
2	16	2	0	2	3	1	1	1	1	1	1	1
		2	0	2	3	1	1	1	1	1	1	1
3	17	0	0	0	2	3	3	3	3	3	2	1
		0	0	0	2	3	3	3	3	3	2	1
3	18	0	0	2	3	3	3	2	1	1	1	2
		0	0	2	3	3	3	2	1	1	1	1
3	19	0	0	1	2	3	3	3	3	2	2	2
		0	0	1	2	3	3	3	3	1	1	1
3	20	0	2	2	3	3	3	2	3	3	1	2
		0	2	2	3	3	3	2	3	3	1	1
3	21											
3	22	0	0	0	2	2	3	1	1	1	1	1
		0	0	0	2	2	3	2	1	1	1	1
3	23	0	0	1	2	2	3	3	3	1	1	1
		0	0	1	2	2	3	3	3	1	1	1
3	24	0	0	0	2	3	3	3	1	1	1	1
		0	0	0	2	3	3	3	1	1	1	1

FIG. 4

TREATMENT AND PREVENTION OF MUCOSITIS IN CANCER PATIENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

The application claims benefit of priority from U.S. Provisional Application No. 60/352,674, filed Jan. 29, 2002 and U.S. Provisional Application No. 60/313,081, filed Aug. 16, 2001, each of which is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

The invention relates to the field of treatment and prevention of disease.

Oral ulcerative mucositis is a common, painful, dose-limiting side effect of drug and radiation therapy for cancer. The disorder is characterized by breakdown of the oral mucosa, which results in the formation of ulcerative lesions. The lesions that result cause inflammatory and ulcerative changes that result in pain and loss of function. Consequently, patients with mucositis often require an alteration in their diets and medication to manage pain. In addition, the presence of mucositis also influences other health and economic outcomes such as medication use, febrile days, use of total parenteral nutrition, length of hospital stay, and total hospital charges. The risk of mucositis often influences the choice of drug and dose to be used in the treatment of a patient and may preclude what is considered to be the optimum anti-cancer regimen. Patients who receive myeloablative therapy are at risk for local and systemic infection. Since the mouth is rich in indigenous microbiota, the loss of mucosal integrity associated with mucositis provides a portal of entry for invading bacteria at a time when a patient's resistance to infection is highly compromised because of chemotherapy-induced neutropenia. In fact, the mouth is the most frequently identified site of origin of systemic infection among granulocytopenic cancer patients.

Mucositis occurs to some degree in more than one third of all patients receiving anti-neoplastic drug therapy. The frequency and severity are significantly greater among patients who are treated with induction therapy for leukemia or with many of the conditioning regimens for bone marrow transplant. Among these individuals, moderate to severe mucositis (ulceration) is common in more than three-quarters of patients.

Patients who receive radiation therapy for tumors of the head and neck are also at high risk for oral mucositis. The frequency and severity of mucosal injury is a function of the total amount of radiation, the schedule of radiation delivery, and the concomitant use of chemotherapy. Increasing the rate of radiation exposure results in a higher incidence of mucositis. While the increasing trend of adding chemotherapy to the radiation regimen results in an improved tumor outcome, many of these protocols are highly stomatotoxic. Mucositis is often of such severity as to necessitate a break in treatment to allow the oral tissues to recover. Such interruptions reduce the overall effectiveness of therapy.

Clinically mucositis progresses through four stages:

1. An initial stage which is characterized by inflammatory changes of erythema and edema. Localized islands of hyperkeratosis may also been seen. This stage is symptomatically mild and may be successfully palliated by topical anesthetics.
2. Subsequently the mucosa breaks down and becomes eroded and atrophic with increasingly significant inflammatory changes. This stage is increasingly painful and may require systemic analgesic therapy in the form of NSAIDs or oral narcotics for adequate palliation.
3. The third stage of mucositis is the most symptomatic. Full thickness ulcers of the mucosa cause severe discomfort necessitating parenteral narcotic therapy. In addition, in the myelosuppressive patient, these ulcerations provide a systemic portal of entry for the oral microflora often leading to bacteremia and sepsis. Antimicrobial intervention is then required.
4. Finally, spontaneous healing occurs about 2–3 weeks after cessation of anti-neoplastic therapy.

Historically mucositis was viewed as a process that was the sole result of epithelial damage. It was believed that the non-specific toxic effects of chemotherapy or radiation caused DNA damage to the rapidly dividing cells of the mucosal basal epithelium. This resulted in cell death, atrophic changes in the mucosa, and ulceration. However, four lines of observation suggested a biologic complexity that extended beyond an epithelial etiology. First, electron microscopic studies demonstrated damage to the endothelium and connective tissue that significantly preceded epithelial breakdown. Second, peripheral blood levels of pro-inflammatory cytokines increased proportionately when non-hematologic toxicities were observed. Third, attenuation of pro-inflammatory cytokine production and expression resulted in the amelioration of experimental mucositis. And fourth, alteration of the local environment by reducing its bacterial load and maintaining salivary function reduced the severity of mucositis.

The condition appears to represent a sequential interaction of oral mucosal cells and tissues including connective tissue, endothelium, epithelium, and inflammatory cells, pro-inflammatory cytokines, and local environmental factors such as bacteria and saliva. Damage to epithelial and connective tissue induces the release of inflammatory cytokines leading to mucosal damage. Additionally, both direct and indirect effects on epithelial cells result in either apoptotic or necrotic changes of basal epithelial cells; differentiation into new epithelial cells is halted. The arrest of epithelial cell renewal leads to atrophy followed by ulceration.

The findings appear to represent 'downstream' events, which result as a consequence of activation of at least two primary pathways: the transcription factor NF-κB and the ceramide pathway. It appears that reactive oxygen species (free radicals) generated by either chemotherapy or radiation are capable of initiating activation of both of these pivotal pathways in leading to mucositis.

Standard therapy for mucositis is predominantly palliative, including application of topical analgesics such as lidocaine and/or systemic administration of narcotics and antibiotics. Currently, there is no approved treatment for mucositis. There is, thus, a need for a method for treating and preventing mucositis.

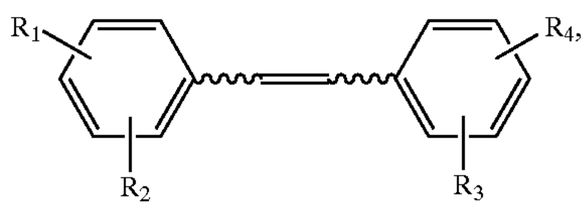
SUMMARY OF THE INVENTION

The invention provides a method for the treatment or prevention of mucositis in an individual undergoing or preparing to undergo cancer treatment.

In one aspect, the invention features a method for the treatment or prevention of mucositis including administering a therapeutically effective amount of an inhibitor of NF-κB to an individual undergoing or preparing to undergo a treatment for cancer. In preferred embodiments, the treatment for cancer is radiation therapy or chemotherapy. In

another embodiment, the mucositis is of the gastrointestinal tract, e.g., of the mouth, esophagus, or stomach. In other preferred embodiments, the inhibitor is administered topically, e.g., as a rinse, troche, or gel. In yet other embodiments, the inhibitor is administered orally or by intraperitoneal injection. Preferably, the inhibitor is administered in a pharmaceutically acceptable carrier, e.g., physiological saline or sterilized water.

In preferred embodiments, the inhibitor is a compound having the formula:



(I)

where R_1 and R_4 are OH, and R_2 and R_3 are independently OH or H, provided that when R_1 and R_2 are both OH, R_1 and R_2 cannot be disposed ortho to one another, and when R_3 and R_4 are both OH, R_3 and R_4 cannot be disposed ortho to one another. The compounds of formula I may be cis or trans.

In other embodiments, the inhibitor is selected from the group consisting of resveratrol, lactacystin, epigallocatechin, curcumin, pyrrolidine dithiocarbamate, herbamycin A, idoxifene, raloxifene, droloxifene, tiremifene, and tamoxifen. Preferably, inhibitors are administered in substantially pure form.

A combination of two or more inhibitors or an inhibitor and another agent, e.g., an analgesic or antibiotic, may also be administered in the methods described herein.

By "treatment" is meant the medical management of a patient with the intent that a cure, stabilization, or amelioration of mucositis will result.

By "prevention" is meant the medical management of a patient with the intent that the patient does not develop mucositis or develops mucositis with reduced severity.

By "therapeutically effective amount" is meant an amount sufficient to produce a preventative, healing, curative, stabilizing, or ameliorative effect.

By "inhibition of NF-κB" is meant inhibition of the activation or action of NF-κB. Inhibition occurs, for example, by blocking activation of NF-κB by reactive oxygen species, by inhibiting proteolysis of the ankyrin repeats in NF-κB, by blocking binding of activated NF-κB to DNA, by blocking transport of NF-κB to the nucleus, by promoting removal of NF-κB from the nucleus, by blocking phosphorylation or degradation of IκB proteins, by upregulating or increasing the concentration of IκB proteins, by inhibiting proteasome degradation of IκB proteins, by inhibiting proteasome modification of NF-κB proteins, or by downregulating or decreasing the concentration of NF-κB.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph of the mean mucositis scores of control hamsters and hamsters treated with 1 mM and 5 mM of resveratrol as a function of days after exposure to radiation.

FIG. **2** is a bar graph showing the number of days, as a percentage, that control hamsters and hamsters treated with 1 mM and 5 mM of resveratrol had a mucositis score of 3 or more.

FIG. **3** is a table listing statistical data for comparison between control hamsters and hamsters treated with 1 mM and 5 mM of resveratrol.

FIG. **4** is a table listing the mucositis scores for control hamsters and hamsters treated with 1 mM and 5 mM resveratrol.

DETAILED DESCRIPTION OF THE INVENTION

Resveratrol (trans-3,4',5-trihydroxystilbene) can be used therapeutically to attenuate mucositis, as disclosed in U.S. Application Ser. No. 60/313,081, hereby incorporated by reference. Resveratrol is a polyphenolic phytoalexin that is found in grapes, fruits, and root extracts of the weed Polygonum cuspidatum. Resveratrol is isolated from grapes predominantly in the trans form. It is a non-flavinoid polyphenol that demonstrates a number of biologic activities including being anti-inflammatory, an anti-oxidant, modulating cell growth, and being anticarcinogenic (Stojanovic et al. Arch Biochem Biophy 2001, 391:79–89). By suppressing the induction of phosphorylation and nuclear translocation of p65 subunit by tumor necrosis factor-alpha (TNF-α), resveratrol blocked the activation of NF-κB (Manna et al. J. Immunol. 2000, 164:6509–19). Since activation of NF-κB by radiation therapy or chemotherapy in cancer patients leads to mucositis, compounds that inhibit the activation or action of NF-κB may be effective in treating or preventing mucositis.

Accordingly, the invention features a method for the treatment or prevention of mucositis. This method is based on the administration of a therapeutically effective amount of an inhibitor of NF-κB to a patient undergoing or about to undergo radiation or chemotherapy treatments for cancer.

Since resveratol has shown efficacy in treating mucositis, other hydroxystilbenes, e.g., the compounds of formula I, may show similar or greater efficacy.

Additional compounds that are known to inhibit NF-κB include, without limitation, α-lipoic acid (Sen et al., 1998; Suzuki et al., 1992), α-tocopherol (Islam et al., 1998), Anetholdithiolthione (ADT) (Sen et al., 1996), Butylated hydroxyanisole (BHA) (Israel et al., 1992; Schulze-Osthoff et al., 1993), Cepharanthine (Okamoto et al., 1994), Caffeic Acid Phenethyl Ester (3,4-dihydroxycinnamic acid, CAPE) (Natarajan et al., 1996), Catechol Derivatives (Suzuki et al., 1994), Diethyldithiocarbamate (DDC) (Schreck et al., 1992b), Deferoxamine (Sappey et al., 1995), Dihydrolipoic Acid (Suzuki et al., 1995), Disulfiram (Schreck et al., 1992b), Dimethyldithiocarbamates (DMDTC) (Pyatt et al., 1998a), Curcumin (Diferulolylmethane) (Singh and Aggarwal, 1995b), Ebselen (Schreck et al., 1992b), EPC-K1 (phosphodiester compound of vitamin E and vitamin C) (Hirano et al., 1998) Epigallocatechin-3-gallate (EGCG; green tea polyphenols) (Lin et al., 1997; Yang et al.,1998), Ethylene Glycol Tetraacetic Acid (EGTA) (Janssen et al., 1999), Gamma-glutamylcysteine synthetase (gamma-GCS) (Manna et al., 1999), Glutathione (Cho et al., 1998; Schreck et al., 1992b), L-cysteine (Mihm et al., 1991) Lacidipine (Cominacini et al., 1998), Manganese Superoxide Dismutase (Mn-SOD) (Manna et al., 1998), Melatonin (Gilad et al., 1998; Mohan et al., 1995), N-acetyl-L-cysteine (NAC) (Schreck et al., 1991), Nordihydroguaiaritic acid (NDGA) (Brennan et al., 1998; Israël et al.,1992; Schulze-Osthoff et al., 1993; Staal et al., 1993), Orthophenanthroline (Schreck et al., 1992b), Phenylarsine oxide (PAO, tyrosine phosphatase inhibitor) (Arbault et al., 1997), Pyrrolidinedithiocarbamate (PDTC) (Schreck et al., 1992a), Quercetin (Musonda and Chipman, 1998), Rotenone (Schulze-Osthoff et al., 1993), S-allyl-cysteine (SAC, garlic compound) (Geng et al., 1997), Tepoxalin (5-(4-chlorophenyl)-N-

hydroxy-(4-methoxyphenyl) -N-methyl-1H -pyrazole-3-propanamide) (Kazmi et al., 1995), Vitamin C (Staal et al., 1993), Vitamin E derivatives (Suzuki and Packer, 1993a), α-torphryl succinate (Staal et al., 1993; Suzuki and Packer, 1993b), α-torphryl acetate (Suzuki et al., 1993a), PMC (2,2,5,7,8-pentamethyl-6-hydroxychromane) (Suzuki et al., 1993a), Peptide Aldehydes: ALLnL (N-acetyl-leucinyl-leucinyl-norleucinal, MG101), LLM (N-acetyl-leucinyl-leucinyl-methional), Z-LLnV (carbobenzoxyl-leucinyl-leucinyl-leucinal, MG132) (Palombella et al., 1994; Grisham et al., 1999; Jobin et al., 1998a), Lactacystin, β-lactone (Fenteany et al., 1998; Grisham et al., 1999), Boronic Acid Peptide (Grisham et al., 1999; Iqbal et al., 1995), Ubiquitin Ligase Inhibitors (Yaaron et al., 1997), Cyclosporin A (Frantz et al., 1994; Marienfield et al., 1997; McCaffrey et al. 1994; Meyer et al., 1997; Wechsler et al., 1994), FK506 (Tacrolimus) (Okamoto et al., 1994; Venkataraman et al., 1995), Deoxyspergualin (Tepper et al., 1995), APNE (N-acetyl-DL-phenylalanine-β-naphthylester) (Higuchi et al., 1995), BTEE (N-benzoyl L-tyrosine-ethylester) (Rossi et al., 1998), DCIC (3,4-dichloroisocoumarin), DFP (diisopropyl fluorophosphate), TPCK (N-α-tosyl-L-phenylalanine chloromethyl ketone), TLCK (N-α-tosyl-L-lysine chloromethyl ketone) (D'Acquisto et al., 1998), Aspirin, sodium salicylate (Frantz and O'Neill, 1995; Kopp and Ghosh, 1994; Yin et al., 1998), BAY-117821 (E3((4-methylphenyl)-sulfonyl)-2-propenenitrile), BAY-117083 (E3((4-t-butylphenyl)-sulfonyl)-2-propenenitrile), Cycloepoxydon, 1-Hydroxy-2-hydroxymethyl-3-pent-1-enylbenzene (Gehrt et al., 1998), Extensively oxidized low density lipoprotein (ox-LDL), 4-Hydroxynonenal (HNE) (Brand et al., 1997; Page et al., 1999), Ibuprofen (Palayoor et al., 1999), Nitric Oxide (NO) (Katsuyama et al., 1998; Matthews et al., 1996), Prostaglandin A1 (Rossi et al., 2000), Sanguinarine (pseudochelerythrine, 13-methyl-[1,3]-benzodioxolo-[5,6-c]-1,3-dioxolo-4,5 phenanthridinium) (Chaturvedi et al., 1997), Sulfasalazine (Wahl et al., 1998), Sulindac (Yamamato et al., 1999), YopJ (encoded by *Yersinia pseudotuberculosis*) (Schesser et al., 1998), α-melanocyte-stimulating hormone (α-MSH) (Manna and Aggarwal, 1998a), β-lapachone (Manna et al., 1999a), Capsaicin (8-methyl-N-vanillyl-6-nonenamide) (Singh et al., 1996b), Core Protein of Hepatitis C virus (HCV) (Shrivastava et al., 1998), Diamide (tyrosine phosphatase inhibitor) (Toledano and Leonard, 1991; Singh and Aggarwal, 1995a), Emodin (3-methyl-1,6,8-trihydroxyanthraquinone) (Kumar et al., 1998), Erbstatin (tyrosine kinase inhibitor) (Natarajan et al., 1998), Estrogen (E2) (Sun et al., 1998), Fungal gliotoxin (Pahl et al., 1996), Genistein (tyrosine kinase inhibitor) (Natarajan et al., 1998), IL-13 (Manna and Aggarwal, 1998b), Leflunomide metabolite (A77 1726) (Manna and Aggarwal, 1999), Pervanadate (tyrosine phosphatase inhibitor) (Singh and Aggarwal, 1995a; Singh et al., 1996a), Phenylarsine oxide (PAO, tyrosine phosphatase inhibitor) (Mahboubi et al., 1998, Singh and Aggarwal, 1995a), Resiniferatoxin (Singh et al., 1996), Sesquiterpene lactones (parthenoide) (Hehner et al., 1998), β-amyloid protein (Bales et al., 1998), Glucocorticoids (dexametasone, prednisone, methylprednisolone) (Auphan et al., 1995; Brostjan et al., 1996; Ray and Prefontaine, 1994; Scheinman et al., 1995), IL-10 (Ehrlich et al., 1998; Lentsch et al., 1997), IL-11 (Trepicchio and Dorner, 1998), Leptomycin B (LMB) (Rodriguez et al., 1999), NLS Cell permeable peptides (Lin et al., 1995), o,o'-bismyristoyl thiamine disulfide (BMT) (Shoji et al., 1998), ADP ribosylation inhibitors (nicotinamide, 3-aminobenzamide) (Le Page et al., 1998), Atrial Natriuretic Peptide (ANP) (Gerbes et al., 1998), Atrovastat (HMG-CoA reductase inhibitor) (Bustos et al., 1998; Hemandez-Presa et al., 1998), Calcitriol (1a,25-dihydroxyvitamine D3) (Harant et al., 1998), Clarithromycin (Miyanohara et al., 2000), Diamide (Toledano and Leonard, 1991), E3330 (quinone derivative) (Hiramoto et al., 1998), Glycyrrhizin (Wang et al., 1998), Herbimycin A (Iwasaki et al., 1992; Mahon and O'Neill,1995), Hypericin (Bork et al., 1999), Hydroquinone (HQ) (Pyatt et al., 1998b), IL-4 (Manna and Aggarwal 1999), IkB-like proteins (encoded by ASFV) (Powell et al., 1996; Revilla et al., 1998), KT-90 (morphine synthetic derivative) (Sueoka et al., 1998), Metals (chromium, cadmium, gold, mercury, zinc, arsenic) (Shumilla et al., 1998; Yang et al., 1995), Mevinolin, 5'-methylthioadenosine (MTA) (Law et al., 1992), N-ethyl-maleimide (NEM) (Toledano and Leonard, 1991), Nicotine (Sugano et al., 1998), Pentoxifylline (1-(5'-oxohexyl) 3,7-dimetylxanthine, PTX) (Biswas et al., 1993; Wang et al., 1997), Phenyl-N-tert-butylnitrone (PBN) (Kotake et al., 1998), Pituitary adenylate cyclase-activating polypeptide (PACAP) (Delgado et al., 1998), Pyrithione (Kim et al., 1999), Quinadril (ACE inhibitor) (Bustos et al., 1998; Hernandez-Presa et al., 1998), Ribavirin (Fiedler et al., 1996), Secretory leukocyte protease inhibitor (SLPI) (Jin et al., 1997), Serotonin derivatives (N-(p-coumaroyl) serotonin, SC) (Kawashima et al., 1998), Silymarin (Saliou et al., 1998), Vascular endothelial growth factor (VEGF) (Oyama et al., 1998; Gabrilovich et al., 1998), Vasoactive intestinal peptide (VIP) (Delgado et al., 1998), D609 (phosphatidylcholine-phospholipase C inhibitor) (Bergmann et al., 1998), RO31-8220 (PKC inhibitor) (Bergmann et al., 1998), SB203580 (p38 MAPK inhibitor) (Bergmann et al., 1998), Triptolide (PG490, extract of Chinese herb) (Qiu et al., 1999), LY294,002 (Sizemore et al., 1999), Mesalamine (Egan et al., 1999), Wortmannin (fungal metabolite) (Manna and Aggarwal, 2000), lactacystin, idoxifene, raloxifene, droloxifene, tiremifene, and tamoxifen. Further examples of compounds that inhibit NF-κB are disclosed in Narayanan et al. (U.S. Pat. No. 5,591,840), Bennett et al. (U.S. Pat. No. 6,069,008), Lai et al. (U.S. Pat. No. 6,316,502), Morishita et al. (U.S. Pat. No. 6,262,033), Qabar et al. (U.S. Pat. No. 6,117,896), and lino et al. (U.S. Pub. No. 2001/018441), each of which is hereby incorporated by reference.

Flavinoids, e.g., those found in soybean (such as genestein), can also be used to attenuate mucositis according to the invention. Among other possible flavinoids that can be used in the invention are galloyl flavonol glycosides such as quercetin or kaempferol.

Topical application is preferred, but compounds can be administered using any standard means for administering therapeutic compounds, including, without limitation, oral, sublingual, intravenous, and intraperitoneal injection. Dosages and timing of administration can be determined using routine methods for such determination, e.g. a therapeutically effective amount is administered one, two, or three times a day. The compounds may be administered, for example, at any time before, during, or after radiation or chemotherapy. Treatment may be continued as long as necessary.

EXAMPLE 1

Animal Model of Treatment of Mucositis with Resveratrol.

Hamster models of chemotherapy-induced mucositis and radiation-induced mucositis have been developed. In the latter model, specific doses of acute radiation were targeted to the designated mucosa, with protection of other areas by

a customized lead shield. The reproducibility of the model has been validated, with the consistent appearance of ulcerative mucositis between days 15 and 18 following radiation. Using this model, the efficacies of various topical agents have been tested for their abilities to modify the course of radiation-induced mucositis.

Project Rationale and Protocol

Study Parameters. This study analyzed resveratrol in both topical and intraperitoneal dosing at concentrations of 1 mM and 5 mM. The control group was dosed topically with water.

Induction of mucositis by an irradiation regimen. An acute radiation dose of 40 Gy on day 0 was administered in order to produce severe mucositis around day 15. The use of acute radiation to induce mucositis was preferable to the use of either fractionated radiation or chemotherapy for these initial studies. The acute model had little systemic toxicity, resulting in fewer animal deaths. This fact permitted the use of smaller groups in the initial studies. The acute model has been used successfully to demonstrate the presence or absence of efficacy for a large number of compounds. The acute radiation model is therefore appropriate as an initial protocol for screening diverse families of compounds.

Mucositis Evaluation

The grade of mucositis was scored, starting from day 6 following irradiation (which occurs on day 0), and for every second day thereafter, through and including day 20. The effect on mucositis of each drug treatment compared to placebo was assessed according to the following parameters:

The difference in the number of days hamsters in each group have severe (score ≧3) mucositis. On each Evaluation Day, the number of animals with a blinded mucositis score of >2 in each drug treatment group, was compared to the control group. Differences were analyzed on a daily as well as a cumulative basis. Successful treatment was considered a statistically significant lower number of hamsters with a score ≧3 in a drug treatment group, versus control as determined by chi-square analysis.

The rank sum differences in daily mucositis scores. For each day of evaluation, the scores of the control group were compared to those of the treated group using the non-parametric rank sum analysis. Treatment success was considered as a statistically significant lowering of scores in the treated group on 2 or more days from day 8 to day 20.

Animals

Male Golden Syrian hamsters (Charles River Laboratories, Wilmington, Mass. or Harlan Sprague Dawley, Indianapolis, Ind.), aged 5 to 6 weeks, with body weight approximately 90 g at project commencement, were used. Animals were individually numbered using an ear punch and housed in small groups of approximately 6 animals per cage. Animals were acclimatized for at least one week prior to project commencement. During this period, the animals were observed daily in order to reject animals that presented poor condition.

Animal Randomization and Allocations.

This study used forty (40) hamsters that were randomly divided into five groups of eight animals per group. Each group was assigned a different treatment as follows:

Group 1	Animals 1–8	topical, tid	water
Group 2	Animals 9–16	intraperitoneal, qd	1 mM Resveratrol
Group 3	Animals 17–24	intraperitoneal, qd	5 mM Resveratrol
Group 4	Animals 25–32	topical, tid	1 mM Resveratrol
Group 5	Animals 33–40	topical, tid	5 mM Resveratrol

Mucositis Induction

Mucositis was induced using an acute radiation protocol. A single dose of radiation (40 Gy/dose) was administered to all animals on Day 0. Radiation was generated with a 250 kilovolt potential (15 mA) source at a focal distance of 50 cm, hardened with a 0.35 mm Cu filtration system. Irradiation targeted the left buccal pouch mucosa at a rate of 121.5 cGy/minute. Prior to irradiation, animals were anesthetized with an intraperitoneal injection of sodium pentobarbital (80 mg/kg). The left buccal pouch was everted, fixed, and isolated using a lead shield.

Dosing and Drug Application

The test compounds were kept frozen and protected from light when not in use during the entire study. Each day of dosing, an aliquot of test compound was removed from the plastic bottles using a sterile syringe, and 0.2 ml of the compound was injected into each animal in groups 2 and 3. Intraperitoneal (IP) dosing was performed once per day from day −1 to day 20.

Topical dosing was performed 3 times per day for animals in groups 1, 4 and 5. A needleless tuberculin syringe, containing 0.2 ml of the test compound or water, was inserted into the left cheek pouch and the drug deposited into the pouch.

All hamsters were weighed daily and their survival recorded, in order to assess possible differences in animal weight among treatment groups as an indication for mucositis severity and/or possible toxicity resulting from the treatments.

Mucositis Evaluation

Starting on Day 6 of each study and then every second day thereafter (Days 8, 10, 12, 14, 16, 18, and 20), animals were photographed and evaluated for mucositis. Parameters to be measured include the mucositis score, weight change, and survival. For the evaluation of mucositis, the animals were anesthetized with inhalation anesthetics, and the left pouch everted. Mucositis was scored visually by comparison to a validated photographic scale, ranging from 0 for normal, to 5 for severe ulceration (clinical scoring). In descriptive terms, this scale was defined as follows:

Score:	Description:
0	Pouch completely healthy. No erythema or vasodilation
1	Light to severe erythema and vasodilation. No erosion of mucosa
2	Severe erythema and vasodilation. Erosion of superficial aspects of mucosa leaving denuded areas. Decreased stippling of mucosa.
3	Formation of off-white ulcers in one or more places. Ulcers may have a yellow/gray due to pseudomembrane. Cumulative size of ulcers should equal about ¼ of the pouch. Severe erythema and vasodilation.
4	Cumulative seize of ulcers should equal about ½ of the pouch. Loss of pliability. Severe erythema and vasodilation.
5	Virtually all of pouch is ulcerated. Loss of pliability (pouch can only partially be extracted from mouth)

A score of 1–2 was considered to represent a mild stage of the disease, whereas a score of 3–5 was considered to indicate moderate to severe mucositis. Following visual scoring, a photograph was taken of each animal's mucosa using a standardized technique. At the conclusion of the experiment, all films were developed and the photographs randomly numbered. At least two independent trained observers graded the photographs in blinded fashion using the above-described scale (blinded scoring).

Assessment of Results

Statistical differences between treatment groups were determined using Student's t-test, Mann-Whitney U test and chi-square analysis with a critical value of 0.05.

Results

The results of the control and IP experiments are shown in FIGS. **1–4**. The data in FIG. **1** show the mean mucositis score as a function of days after exposure to radiation for control hamster and hamsters treated with 1 mM and 5 mM of resveratrol (IP administration). As illustrated in FIG. **2**., treatment with resveratrol reduced the severity of mucositis compared to the control. Treatment with 1 mM resveratrol was more effective than treatment with 5 mM of resveratrol. The percentage of days where hamsters had a mucositis score of less than three was reduced from 46.0% for the control to 31.2% for treatment with 5 mM and to 21.6% for treatment with 1 mM of resveratrol (FIG. **3**). FIG. **4** lists the individual scores for each hamster in groups 1–3, as defined above, as a function of time.

The results of the experiments on topical application of resveratrol, although not statistically significant, indicated a trend of efficacy.

EXAMPLE 2

Synthesis of Hydroxystilbene Derivatives.

Compounds of formula I above can be synthesized by methods known in the art, for example, by the methods of Moreno-Manas et al. Anal. Quim. 1985, 81:157–161; Jeandet et al. Am. J. Enol. Vitic. 1991, 42:41–46; Goldberg et al. Anal. Chem. 1994, 66:3959–3963; and March *Advanced Organic Chemistry*, 4th ed., Wiley: N.Y., 1992.

Other Embodiments

Modifications and variations of the described methods of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific desirable embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention, which are obvious to those skilled in the art, are intended to be within the scope of the invention.

All publications, patents, and patent applications mentioned in this specification are hereby incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually to be incorporated by reference.

Other embodiments are within the claims.

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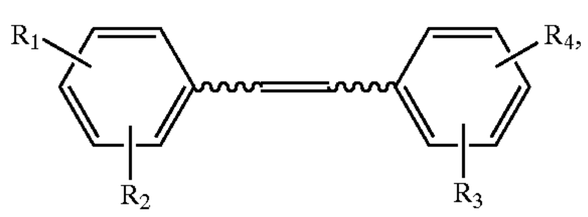
What is claimed is:

1. A method for the treatment or reduction of mucositis comprising administering to an individual undergoing or preparing to undergo a treatment for cancer a therapeutically effective amount of a compound having the formula:



where R_1 and R_4 are OH, and R_2 and R_3 are independently OH or H, provided that when R_1 and R_2 are both OH, R_1 and R_2 cannot be disposed ortho to one another, and when R_3 and R_4 are both OH, R_3 and R_4 cannot be disposed ortho to one another.

2. The method of claim **1**, wherein the treatment for cancer is radiation therapy.

3. The method of claim **1**, wherein the treatment for cancer is chemotherapy.

4. The method of claim **1**, wherein the mucositis is of the gastrointestinal tract.

5. The method of claim **4**, wherein the mucositis is of the mouth, esophagus, or stomach.

6. The method of claim **1**, wherein the compound is administered topically.

7. The method of claim **6**, wherein the compound is administered in a rinse, troche, or gel.

8. The method of claim **1**, wherein the compound is administered orally or by intraperitoneal injection.

9. The method of claim **1**, wherein the compound is administered in a pharmaceutically acceptable carrier.

10. The method of claim **1**, wherein the compound is resveratrol.

11. The method of claim **1**, wherein the compound is cis.

12. The method of claim **1**, wherein the compound is trans.

* * * * *